Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work. Supplement to: H Park, DY Kang, JM Ahn, et al. "Rationale and design of the ADAPT-TAVR trial: a randomized comparison of edoxaban and dual antiplatelet therapy for prevention of leaflet thrombosis and cerebral embolization after transcatheter aortic valve replacement"

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Appendix Table 1. Definitions of Clinical Endpoints.

All clinical endpoints are adjudicated according to current VARC-2[1] and the NeuroARC[2] definitions. Each of clinical endpoints is defined as follows:

Endpoint	**Definition**
Death	All-cause mortality was used rather than cardiac mortality to eliminate the need for possibly difficult adjudication of causes of death, especially given the relatively low mortality expected. In addition, the cause of death will be adjudicated as being due to cardiovascular causes or non-cardiovascular causes. Cardiovascular death includes any of the following criteria: • Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or non-structural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause Non-cardiovascular death is defined as any death in which the primary cause of death is clearly related to another condition (e.g., trauma, cancer, or suicide)
MI	MI (non-procedural) is defined as any one of the following criteria: (1) detection of rise and/or fall of cardiac biomarkers (preferably troponin) with a least one value above the 99th percentile URL, together with the evidence of myocardial ischemia with at least one of the following: a) symptoms of ischemia, b) ECG changes indicative of new

	ischemia (new ST-T changes or new LBBB), c) new pathological Q-waves in at least two contiguous leads, or d) imaging evidence of a new loss of viable myocardium or new wall motion abnormality, (2) sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia and accompanied by presumably new ST elevation or new LBBB, and/ or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood (3) pathological findings of an acute myocardial infarction
Stroke and TIA	**Diagnostic criteria** • Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Stroke: duration of a focal or global neurological deficit >24 h or <24 h if available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death • TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct Confirmation of the diagnosis by at least one of the following: • Neurologist or neurosurgical specialist • Neuroimaging procedure (CT or brain MRI), but stroke may be diagnosed on clinical grounds alone **Stroke classification** • Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue • Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage

	• A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic **<u>Stroke definitions</u>** • Disabling stroke: a modified Rankin Scale (mRS) score of ≥2 at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline • Non-disabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline
Bleeding events	Life-threatening or disabling bleeding is defined as any one of the following criteria: • Fatal bleeding (BARC type 5) • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) • Overt source of bleeding with drop in hemoglobin >5 g/dL or whole blood or packed red blood cells (RBCs) transfusion >4 units* (BARC type 3b) Major bleeding (BARC type 3a) • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery and does not meet criteria of life-threatening or disabling bleeding Minor bleeding (BARC type 2 or 3a, depending on the severity) • Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling, or major

Appendix Table 2. Trial-Specific Standardized Cardiac CT Protocol

Items	Minimum requirements of acquisition protocols
CT scanners	GE Healthcare: 64 channel or above (e.g., Optima 660, Revolution HD/GSI, Revolution CT) Philips Healthcare: 64 channel or above (e.g., Ingenuity, iCT Elite, IQon Spectral CT) Siemens Healthineers: dual source or above (e.g., Somatom Definition AS, AS+, or Flash) Toshiba 320 or above (e.g., Aquilion ONE, Aquilion ONE Vision)
Minimum gantry rotation time (ms)	350 ms or below
Kernal	Manufacturer's recommendation
kVp, mAs, AEC	Manufacture's setting (site can utilize institutional protocols for kVp, mAs, and automatic exposure control).
ECG-gating	Imaging of the aortic root must use ECG-synchronization, using either two separate acquisitions (ECG-synchronized for the aortic root and non-gated for the aorta) or single ECG-synchronized acquisition of the entire volume
Scan coverage	Scan to include at least the aortic arch and whole heart (from the upper wall of aortic arch to lower cardiac border) in cranio-caudal direction
Patient position	The preferred subject position is supine with arms raised above the head and the heart centered within the gantry. Special attention should be paid to ensure proper positioning and firm contact of ECG leads to ensure a high R-peak amplitude and low baseline noise.
Image Reconstruction & Slice thickness	Iterative image reconstruction methods/algorithms are recommended according to manufacturers' setting and should meet the following minimum requirements: - Slice thickness should be ≤ 1.0 mm. - Recommendation for single source CT scanners (GE, Toshiba, Philips): 0.6 mm slices with 0.3 mm overlap and iterative reconstruction for evaluation at 5% intervals within the 0%-95% RR range - Recommendation of dual-source CT scanners (Siemens): 0.5 mm slices with 0.25 mm overlap with iterative reconstruction for evaluation at 10% intervals within the 0%-90% RR range

	- Recommended optimal timing: at lower heart rates (<65 bpm), the optimal timing is during late-diastole, while at higher heart rates (>65 to 70 bpm) the optimal timing is more frequently (but not always) during end-systole.
Spatial Resolution	≤0.5 × 0.5 mm in x–y plane and ≤1 mm in z-axis
Display FOV	Adjusted according to the heart size
Matrix	512 × 512
Contrast agent	Non-ionic CT contrast agents should be used.
Contrast Injection (Volume, Rate)	Injection volume: 50-120 cc per institutional protocols. Injection rate: 4-7 cc/s per institutional protocols. Scan timing determination: Bolus tracking (preferred) and test bolus methods should be used.
Others	Heart rate (HR) reduction with β-blockade is not performed.
* Note: The site can modify the abovementioned in the inevitable situation such as emergent patients' care or technical issues in the machines or scanning rooms. In these cases, the images can be used for clinical trials after quality check from Asan Image Metrics staffs.	

Appendix Table 3. Standardized Brain Protocols of DWI, GRE, and FLAIR

Items	Requirements		
	Axial DWI	**Axial GRE**	**Axial 2D FLAIR**
Tesla	1.5–3.0 Tesla		
Coil	Head coil or Neurovascular (NV) coil. The number of channels is 8 or above.		
Sequence	EPI[a]	T2* weighted GRE	TSE[b] and equivalent
FOV	190–250 mm	190–250 mm	190–250 mm
Matrix	128×128 or above	128×128 or above	256×256 or above
Resolution	2.0×2.0mm²	2.0×2.0mm²	2.0×2.0mm²
TR	2000 ms or above	400-1000 ms	6000 ms or above
TE	110 ms or below	15-32ms	100-140 ms
TI	Not available (NA)	NA	2200-2500 ms
Slice thickness	3.0–5.0 mm	3.0–5.0 mm	3.0–5.0 mm
Gap thickness	0–2.5 mm	0–2.5 mm	0–2.5 mm
Diffusion Option (B-value)	At least two b-values of 0 s/㎟ and 1000 s/㎟ should be included. The other b-values such as above 1000s/㎟ are optional).	NA	NA
Parallel Imaging	Recommend (up to 2X)	Recommend (up to 2X)	Recommend (up to 2X)

[a]In the event of significant patient motion, a radial acquisition scheme may be used (e.g. BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.

[b]TSE = turbo spin echo (Siemens & Philips) is equivalent to FSE (fast spin echo; GE, Hitachi, Toshiba)

Appendix Table 4. Cardiac CT Analysis Form

Valvular thrombosis □ Presence □ Absence			
	Location of thrombosis	**Presence**	**Size of thrombosis (mm), if present.**
1	**THV leaflet**	□ Presence □ Absence	
2	**Subvalvular area**	□ Presence □ Absence	
3	**Supravalvular area**	□ Presence □ Absence	
4	**Left ventricle outflow tract (LVOT)**	□ Presence □ Absence	

Leaflet motion based on grade of opening limitation
* Opening limitation = a / b * 100 %
(a= radius of stent frame, b = orthogonal line through the affected leaflet to the center of the frame)

1	**leaflet 1 (right)**	□ Normal (fully opening) □ Mild (<50% reduction) □ Moderate (50%-70% reduction) □ severe (>70% reduction) □ Immobile
	leaflet 2 (left)	□ Normal (fully opening) □ Mild (<50% reduction) □ Moderate (50%-70% reduction) □ severe (>70% reduction) □ Immobile
	leaflet 3 (non)	□ Normal (fully opening) □ Mild (<50% reduction) □ Moderate (50%-70% reduction) □ severe (>70% reduction) □ Immobile

Stent eccentricity (%)

		Long diameter (mm)	**Short diameter (mm)**	**Eccentricity (%)**
1	**At the level of inflow**			
2	**At the level of valvular**			
3	**At the level of outflow**			

Calcification volume

		Yes or No?	**Volume(mm^2)**
1	**At the level of annulus**	□ Yes □ No	
2	**At the level of sinus**	□ Yes □ No	
3	**At the level of Valsalva level**	□ Yes □ No	

Comments

Appendix Table 5. Brain MRI Analysis Form

1. DWI-positive lesions		
	Presence/Number/Volume of Lesion	Assessment and Evaluation
1	Presence of new lesion	☐ Presence ☐ Absence
2	Number of new lesions	
3	Volume of new lesion	
Other Comments (please describe DWI findings):		
2. FLAIR-positive lesions		
	Presence/Number/Volume of Lesion	Assessment and Evaluation
1	Presence of new lesion	☐ Presence ☐ Absence
2	Number of new lesions	
3	Volume of new lesion	
Other Comments (please describe FLAIR findings):		
3. GRE-positive lesions		
	Presence/Number/Volume of Lesion	Assessment and Evaluation
1	Presence of new lesion	☐ Presence ☐ Absence
2	Number of new lesions	
3	Volume of new lesion	
Other Comments (please describe GRE findings):		

References

1. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg* 2012;42:S45-60.
2. Lansky AJ, Messé SR, Brickman AM, et al. Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials. *An Academic Research Consortium Initiative* 2017;69:679-91.